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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,666	11/15/2001	Avi J. Ashkenazi	P2730P1C42	4941

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,666	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 26 August 2003 has been entered in full. Claims 1-118 were cancelled. New claims 119-131 were added. Claims 119-131 are under examination.

The information disclosure statement filed 31 May 2002 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits. However, Blast results cannot be printed on the face of a patent.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 119-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility *for the isolated polypeptide*. The instant claims are drawn to an isolated polypeptide shown in Figure 286 (SEQ ID NO:401), the amino acid sequence of the polypeptide encoded by the full length coding sequence of the cDNA deposited under ATCC accession number 203096 and a chimeric polypeptide.

The specification teaches that DNA62881-1515 sequence encodes a novel factor designated as PRO1185 (SEQ ID NO:401). The specification states that the cDNA clone (DNA62881-1515) that has been identified encodes a novel polypeptide having sequence identity to a glucose repression regulatory protein, tup1 (page 260, lines 17-

21). The specification fails to disclose any information regarding ligands, functional characteristics/mechanisms of action of PRO1185. The specification only proposes a sequence identity with the glucose repression regulatory protein, tup1. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Karp (1998, Bioinformatics 14:753-754) states that functional annotations are propagated repeatedly from one sequence to the next with no record made of the source of a given annotation, leading to a potential transitive catastrophe of erroneous annotations. Incorrect functional predictions can result from a number of causes, including: divergence of function within homologous proteins, confusion or omission of functions across multimodular proteins or simply choosing the strongest homolog as the source of attributed function.

The specification asserts several utilities. The specification states that the PRO polypeptides described herein may be employed as therapeutic agents. The instant invention encompasses methods of screening compounds for PRO agonist and antagonists. Screening assays are designed to identify small molecule drug candidates.

The specification states that nucleotide sequences (or their complement) encoding PRO have various applications in the art including uses as hybridization probes, chromosome and gene mapping and producing knock-out animals. Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In addition, the

specification teaches that PRO polypeptide encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. The specification states that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers and diagnostic determination of the presence of those cancers (page 539, lines 20-25). The specification teaches experiments to determine whether the DNA encoding the PRO polypeptide is over-represented in any of the primary lung or colon cancers or cancer cell lines or breast cancer cell line that were screened. Primary lung cancers were obtained from individuals with tumors. The results of the TaqMan are reported in deltaCt units. One unit corresponds to 1 PCR cycle or approximately a 2 fold amplification relative to normal (page 539, lines 26-41). The specification teaches that primary tumor (human lung tumor) LT3, LT26 and LT30 have deltaCt units of 1.01, 1.66 and 1.58 respectively for PRO1185 (page 552). The specification teaches that human colon cancer CT2 has a deltaCt unit of 1.73 for PRO1185 (page 552).

While the instant specification *may have utility for the polynucleotide*, the instant claims are drawn to the polypeptide. The increased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity or role in cancer. The protein is not specific to one tissue or type of tissue and is not associated with any disease or disorder. In addition, protein expression shows a poor correlation with mRNA expression. The Examiner has cited Haynes *et al.* to demonstrate this. Haynes *et al.* (Electrophoresis 19:1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level and

found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, 2nd paragraph, and Figure 1). Pennica *et al.* (Proc. Natl. Acad. Sci. 95:14717-1422, 1998) provides examples where copy number is amplified but the RNA expression is actually reduced. The relative gene copy number of WISP-2 is greatly amplified in human colon adenocarcinomas but the mRNA expression is significantly low (Figure 6 and Figure 7). Konopka *et al.* (abstract, Proc. Natl. Acad. Sci. 83:4049-52) states that protein expression of the abl polypeptide is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA.

Thus, the claimed invention lacks specific and substantial utility. Processes to screen for receptor agonists and/or antagonists and making antibodies against polypeptides are not specific utilities. They are starting point for further research and investigation to identify or reasonably confirm what the practical use might ultimately be. Agonist/antagonist assays are performed for any receptor-ligand pair when the physiological role of each is unknown. Antibodies can be made to any protein. A specific utility is a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. The assays recited for the polypeptide are general utilities that would be applicable to the broad class of the invention. The specification also states that the protein is useful as a tool for screening compounds as drug candidates for immune function related diseases. The

specification fails to provide a correlation to the predisposition of a particular disease and the polypeptide. For example is PRO1185 mutated, deleted or overexpressed in the disease? Further experimentation is required before this asserted utility is substantial.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. Specific and substantial utilities amount to more than a starting point for further research and investigation. It does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptide.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, the instant claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:401, which does not have activity. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the these claims. The claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. While the specification suggests that the instant polypeptide has sequence identity with the glucose repression regulatory protein, tup1, this is not enough to discern a function. As was stated above, knowledge about a protein structure does not provide predictability about function of a structurally related protein. The specification does not teach how to make any variant of the exemplified polypeptides and provides no assay to evaluate the function of any modified polypeptide. There are no working examples of polypeptides less than 100% identical to the polypeptide of SEQ ID NO:401, thus the skilled artisan would not know how to use non-identical polypeptides on the basis of the teachings in the specification unless they possessed some sort of function, which the specification fails to teach.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the lack of knowledge about function of the encompassed polypeptides, the lack of working examples and the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:401, and the breadth of the claims which recite structure without function, it would require undue experimentation to the use the invention.

Claims 119-123, 130 and 131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID NO:401, but not variants. The instant claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:401 with no particular biological activity. Thus the claims are drawn to a genus of polypeptides that are defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recited percent identity. In absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID NO:401, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:401, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to the amino acid sequence of various domains of the peptide disclosed in Figure 286 (SEQ ID NO:401). The specification states that the predicted polypeptide precursor is 198 amino acids long. The specification teaches that the signal peptide is about 1-21 of SEQ ID NO:401 (page 506, lines 1-6). The specification however, fails to identify extracellular and/or transmembrane domains of the instant protein. Thus it is unclear how to discern the amino acid sequence region of the extracellular domain and the extracellular domain lacking its associated signal peptide. For example, how is the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 286 SEQ ID NO:401 different from the amino acid sequence of the polypeptide shown in Figure 286 (SEQ ID NO:401)? The metes and bounds of the instant claims cannot be determined.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
3/17/04

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